Risks and Benefits of Glioblastoma Resection in Older Adults: A Retrospective Austrian Multicenter Study

Christoph Schwartz[1,12], Alexander Romagna[1,13], Harald Stefanits[7], Georg Zimmermann[2,10], Barbara Ladisich[1], Philipp Geiger[1], Julian Rechberger[1], Sophie Winkler[7], Lukas Weiss[3], Gerd Fastner[4], Eugen Trinka[2], Serge Weis[8], Sabine Spiegl-Kreinecker[7], Jürgen Steinbacher[5], Mark McCoy[5], Trenkler Johannes[9], Andreas Gruber[7], Behnam Rezai Jahromi[6], Mika Niemelä[6], Peter A. Winkler[1], Niklas Thon[11]

■ OBJECTIVE: **To assess the prognostic profile, clinical outcome, treatment-associated morbidity, and treatment burden of elderly patients with glioblastoma (GBM) undergoing microsurgical tumor resection as part of contemporary treatment algorithms.**

■ METHODS: **We retrospectively identified patients with GBM ≥65 years of age who were treated by resection at 2 neuro-oncology centers. Survival was assessed by Kaplan-Meier analyses; log-rank tests identified prognostic factors.**

■ RESULTS: **The study population included 160 patients (mean age, 73.1 ± 5.1 years), and the median contrast-enhancing tumor volume was 31.0 cm^3. Biomarker analyses revealed O(6)-methylguanine-DNA methyltransferase–promoter methylation in 62.7% and wild-type isocitrate dehydrogenase in 97.5% of tumors. The median extent of resection (EOR) was 92.3%, surgical complications were noted in 10.0% of patients, and the median postoperative hospitalization period was 8 days. Most patients (60.0%) received adjuvant radio-/chemotherapy. The overall treatment-associated morbidity was 30.6%. The median progression-free and overall survival were 5.4 months (95% confidence interval [CI], 4.6–6.4 months) and 10.0 months (95% CI, 7.9–11.7 months). The strongest predictors for favorable outcome were patient age ≤73.0 years ($P = 0.0083$), preoperative Karnofsky Performance Status Scale score ≥80% ($P = 0.0179$), postoperative modified Rankin Scale score ≤1 ($P < 0.0001$), adjuvant treatment ($P < 0.0001$), and no treatment-associated morbidity ($P = 0.0478$). Increased EOR did not correlate with survival ($P = 0.5046$), but correlated significantly with treatment-associated morbidity ($P = 0.0031$).**

■ CONCLUSIONS: **Clinical outcome for elderly patients with GBM remains limited. Nonetheless, the observed treatment-associated morbidity and treatment burden were moderate in the patients, and patient age and performance status remained the strongest predictors for survival. The risks and benefits of tumor resection in the age of**

Key words
- Adjuvant treatment
- Biomarker
- Elderly
- Glioblastoma multiforme
- Outcome
- Resection
- Treatment-associated morbidity

Abbreviations and Acronyms
BSC: Best supportive care
CI: Confidence interval
EOR: Extent of resection
EORTC/NCIC: European Organisation for Research and Treatment of Cancer and National Cancer Institute of Canada Clinical Trials Group
GBM: Glioblastoma
GTR: Gross total resection
HR: Hazard ratio
IDH: Isocitrate dehydrogenase
KPS: Karnofsky Performance Status Scale
MGMT: O(6)-methylguanine-DNA methyltransferase
MRI: Magnetic resonance imaging
mRS: Modified Rankin Scale
OS: Overall survival
PFS: Progression-free survival
RTx/CTx: Radio-/chemotherapy
TMZ: Temozolomide
WHO: World Health Organization

From the Departments of [1]Neurosurgery, [2]Neurology, [3]Internal Medicine III with Haematology, Medical Oncology, Haemostaseology, Infectiology and Rheumatology, and [4]Radiotherapy and Radio-Oncology and [5]Division of Neuroradiology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria; [6]Department of Neurosurgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland; [7]Department of Neurosurgery, [8]Division of Neuropathology, and [9]Institute of Neuroradiology, Neuromed Campus, Kepler University Hospital, Johannes Kepler University, Linz, Austria; [10]Centre for Cognitive Neuroscience, Paracelsus Medical University, Salzburg, Austria; and [11]Department of Neurosurgery, University Hospital Munich, Ludwig-Maximilians-University, Munich, Germany

To whom correspondence should be addressed: Christoph Schwartz, M.D. [E-mail: c.schwartz@salk.at]

[12]Present address: Department of Neurosurgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland.

[13]Present address: Division of Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

Citation: World Neurosurg. (2020) 133:e583-e591.
https://doi.org/10.1016/j.wneu.2019.09.097

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

1878-8750/$ - see front matter

biomarker-adjusted treatment concepts require further prospective evaluation.

INTRODUCTION

Glioblastoma (GBM) is the most common malignant primary adult brain tumor, and prognosis of patients with GBM remains poor.[1,2] The peak incidence is 64.0 years of age, and a significant proportion of patients are ≥70 years of age.[1,2] Because of demographic developments, an increase in the number of patients can be expected.[3,4] In addition to a poor clinical status, a higher age is the strongest prognostic factor for limited progression-free survival (PFS) and overall survival (OS).[4-8] Moreover, elderly patients with GBM typically have unfavorable biomarkers, comprising a wild-type isocitrate dehydrogenase (IDH 1/2) and unmethylated O(6)-methylguanine-DNA methyltransferase (MGMT)—promoter status.[2,9,10]

Standard treatment at first diagnosis entails maximum safe resection followed by radio-/chemotherapy (RTx/CTx) with temozolomide (TMZ).[2] Older adults usually undergo less invasive treatment to not risk negative therapy-induced effects on outcome. This includes hypofractionated radiation regimens, dose-adapted chemotherapies, and sometimes combinations of both. Patients in poor condition may undergo best supportive care (BSC) only. Recent studies have shown that, in addition to conventional prognostic factors, the molecular profile of tumors can be used to select from these treatment alternatives.[3-8,11-29] Microsurgery's place within this framework remains unclear.[6,18-22] Even though gross total resection (GTR) has been proven to increase OS, little data are available concerning the risks and benefits of resections in older adults.[8,11-18]

This retrospective study by 2 neuro-oncology centers has been performed to assess the prognostic profile, clinical outcome, treatment-associated morbidity, and treatment burden of elderly patients with newly diagnosed GBM, who were found eligible for elective tumor resection as part of contemporary management.

METHODS

Patients

We retrospectively identified all consecutive patients with proven GBM, who had been treated in the neuro-oncology centers of 2 university hospitals between July 2007 and December 2016. All patients had given prior written informed consent to all applied treatments; no study-specific treatments were conducted. The local institutional review boards approved the study.

Inclusion criteria included the following: 1) initial patient age ≥65 years, 2) primary treatment was microsurgical tumor resection, and 3) resections were elective procedures with perioperative cessation of anticoagulation. Patients, who had either undergone emergency surgery, biopsy, or palliative care only, were not included. The last clinical follow-up was August 31, 2018.

Treatment and Follow-Up

In both centers, treatment decisions were made by the interdisciplinary tumor boards. Indication for microsurgical resection was usually seen for patients with a Karnofsky Performance Status Scale (KPS) score ≥60% harboring tumors considered eligible for GTR or at least 70% tumor reduction in case of symptomatic space-occupying effects. Resections were carried out using 5-aminolevulinic acid fluorescence microscopy, intraoperative ultrasound, and neuronavigation to optimize the extent of resection (EOR); intraoperative magnetic resonance imaging (MRI) was available at one center and used in selected cases.

Histopathologic grading including biomarker analyses (i.e., *IDH* 1/2 mutations, MGMT-promotor methylation status, *TERT* mutational status) was conducted per World Health Organization (WHO) classification.[2] Because of the time of study inclusion, the biomarker status was retrospectively assessed in missing cases and not available for all patients.

Clinical follow-up data were extracted from the medical charts and electronic databases. We recorded all applied treatment regimens over the course of the disease and dates of tumor progression and/or death. The patients' clinical risk factors (i.e., age at diagnosis, cardiovascular comorbidities as defined by the classification of the American Society of Anesthesiologists) and treatment-associated morbidity and mortality were recorded. The length of the postoperative hospitalization was documented. The MRI follow-up algorithm—applied at both centers—was as follows: the first postoperative MRI was performed within 72 hours after tumor resection. For patients, who underwent further adjuvant treatment, the next consecutive MRI was performed 4—6 weeks after the end of the RTx or concomitant CTx/RTx (approximately 3 months after surgery). Further clinical follow-up visits including MRI evaluations were then performed in 3-months intervals; tumor progression was assessed by the response assessment in neuro-oncology criteria.[30] In selected cases, O-(2-[18 F]fluoroethyl)-1-tyrosine positron emission tomography scans were additionally applied to differentiate tumor progression from pseudoprogression/treatment-induced changes.[31] Two blinded neuroradiologic staff members (J. S. and M. M.) reevaluated all pre- and postoperative MRI. Calculation of tumor volumes was based on the sum of contrast-enhanced tumor areas in each consecutive sequence in T1-weighted images covering entire tumor extensions. The EOR calculations were based on the difference of pre- and postoperative tumor volumes, as seen on preoperative and immediate postoperative (within 72 hours after surgery) MRI scans.

Statistical Analyses

Death was tumor-related in each case of the patient population. Survival time was defined as the time either to death or last follow-up, whichever occurred first. PFS time was defined as the time to either first recurrence or last follow-up. In both cases, (progression-free) survival times were considered as censored if last follow-up was first. All analyses were carried out using the statistical software package R (R Foundation for Statistical Computing, Vienna, Austria). To assess overall (progression-free) survival and potential associations with a set of variables, which were specified in advance, Kaplan-Meier analyses including confidence intervals (CIs) and corresponding log-rank tests were performed. Asymptotic *P* values are reported; nevertheless, sensitivity analyses revealed that they do not differ substantially from their exact counterparts. The significance level was set to

5.0%. Ordinal and metric variables were transformed to categorical variables either by applying a median split, or by categorizations (i.e., EOR). For the postoperative modified Rankin Scale (mRS), we used the median of the preoperative mRS score, to ensure consistency, and because it was advantageous with respect to subgroup size balance. All variables that showed univariate associations at the 5.0% level were included in a Cox proportional hazards model without interaction terms. Visual inspection of the Kaplan-Meier plots and a test for time-independent hazards, which was conducted by using the function cox.zph within the package survival in R, revealed that there was no substantial indication of nonproportional hazards.[32,33] Therefore, we proceeded with fitting the models and extracting the estimated hazard ratios (HRs) along with corresponding 95% CIs and P values. As a sensitivity analysis, we examined Cox proportional-hazards models using the original instead of the categorized versions of the variables.

RESULTS

Patient and Tumor Characteristics

The patient population consisted of 160 cases (60.0% men), with a mean age at initial diagnosis of 73.1 ± 5.1 years (range, 65–88 years). The median preoperative KPS score was 80% (range, 60%–100%), and the median preoperative mRS score was 1 (range, 0–4). The most common tumor locations were the temporal (n = 61) and frontal (n = 43) lobes. The median preoperative tumor volume was 31.0 cm^3 (range, 3.2–157.6 cm^3). The main signs and symptoms leading to initial diagnosis were worsening of general medical condition (i.e., cognitive impairment) and/or progressive headache in 65 of 160 patients (40.6%), neurologic deficits, with aphasia and hemiparesis being the most common, in 64 of 160 patients (40.0%), and epileptic seizures in 34 of 160 patients (21.3%). Relevant comorbidities (American Society of Anesthesiologists class ≥2) were recorded for 88 of 160 patients (55.0%); most suffered from arterial hypertension, coronary heart disease, and diabetes.

All but 4 patients (97.5%) suffered from GBM with wild-type IDH. None of the analyzed patients had a known precursor lesion on previous MRI scan or had undergone prior tumor resection for a WHO grade II or III glioma at a younger age. A methylated MGMT-promoter status was seen in 74 of 118 tumors (62.7%) and a TERT mutation was seen in 70 of 115 tumors (60.9%). The median Ki67 proliferation index was 30.0% (range, 10.0%–75.0%) (**Table 1**).

Table 1. Study Population and Tumor Characteristics (N = 160)

Variable	Value
Study population	
Age at diagnosis (years)	73.1 ± 5.1
Sex (men)	97/160 (60.6)
Patients with relevant cardiovascular comorbidities	88/160 (55.0)
Preoperative KPS score (%)	80 (60–100)
Preoperative mRS score	1 (0–4)
Postoperative mRS score	2 (0–5)
Postoperative hospital stay (days)	8 (4–52)
Tumor location and volume	
Temporal	61/160 (38.1)
Frontal	43/160 (26.9)
Parietal	17/160 (10.6)
Frontotemporal	9/160 (5.6)
Parietooccipital	9/160 (5.6)
Occipital	7/160 (4.4)
Temporooccipital	7/160 (4.4)
Parietotemporal	2/160 (1.3)
Frontoparietal	5/160 (3.1)
Right side	90/160 (56.3)
Tumor volume (cm^3)	31.0 (3.2–157.6)
Histopathology and molecular markers*	
IDH 1 mutation	4/157 (2.5)
MGMT-promoter methylated	74/118 (62.7)
TERT mutation	70/115 (60.9)
Ki67 proliferation index (%)	30 (10–75)

Values are number of patients/total number of patients (%), mean ± SD, or median (range).
KPS, Karnofsky Performance Status Scale; mRS, modified Rankin Scale, MGMT, O(6)-methylguanine-DNA methyltransferase.
*Not available for all patients.

EOR and Perioperative Morbidity

Postoperative MRI revealed an EOR of ≥95% in 66 of 152 patients (43.4%), an EOR between 70% and 94% in 64 of 152 patients (42.1%), and an EOR <70% in 22 of 152 patients (14.5%). Accordingly, the median calculated EOR was 92.3% (range, 23.2%–100.0%), and the median postoperative tumor volume was 2.4 cm^3 (range, 0.0–26.9 cm^3). For 8 patients, no postoperative MRI (within 72 hours after surgery) was available.

The median postoperative mRS score was 2 (range, 0–5). Eight patients (5.0%) underwent revision surgery for symptomatic postoperative hemorrhage (intraparenchymal: n = 6, subdural: n = 1, and epidural: n = 1). These complications were not associated with larger tumor volumes, lower EOR, or higher age. Moreover, 3 of 160 patients (1.9%) required surgical intervention for cerebrospinal fluid leakage, and 2 of 160 patients (1.3%) were treated for pulmonary embolism. Postoperative new neurologic deficits were seen in 15 of 160 patients (9.4%) (hemiparesis: n = 8, aphasia: n = 4, or both: n = 3). Among these were 3 patients who underwent revision surgery for postoperative hemorrhage. Postoperative delirium was seen in 12 of 160 patients (7.5%). Overall, surgery-related relevant complications were seen in 16 of 160 patients (10.0%).

Adjuvant Treatment

The median time of postoperative hospitalization was 8 days (range, 4–52 days). Most patients (122 of 160; 76.3%) received

Table 2. Surgery and Adjuvant Treatment

Variable	Value
Extent of resection*	
EOR (%)	92.3 (23.2–100.0)
EOR ≥95%	66/152 (43.4)
EOR 70%–94%	64/152 (42.1)
EOR <70%	22/152 (14.5)
Postoperative tumour volume (cm^3)	2.4 (0.0–26.9)
Adjuvant treatment	
RTx/CTx	96/160 (60.0)
RTx only	19/160 (11.9)
CTx only	7/160 (4.4)
Palliative care	38/160 (23.8)
Time to adjuvant treatment after surgery (days)	24 (6–81)

Values are number of patients/total number of patients (%) or median (range).
EOR, extent of resection; RTx, radiotherapy; CTx, chemotherapy.
*Immediate postoperative magnetic resonance imaging was not available for all patients.

adjuvant treatment. In 38 patients (23.7%), no further tumor-specific therapy was initiated, but BSC was performed. The main reasons for BSC were a reduced physical condition and sporadic rejection by patients and/or relatives. The median time from surgery until the start of adjuvant treatment was 24 days (range, 8–81 days). Most patients (n = 96; 60.0%) received RTx/CTx according to the standard EORTC/NCIC Stupp protocol (originally established for patients up to 65 years of age).[2] Nineteen patients (11.9%) underwent hypofractionated RTx alone, and 7 MGMT-methylated patients (4.4%) were treated with TMZ chemotherapy. Adjuvant CTx with TMZ was associated with hematologic complications in 20 of 103 patients (19.4%), necessitating a dose reduction in 6 of 103 patients (5.8%) and a discontinuation of CTx in 14 of 103 patients (13.6%). At disease progression, 17 patients (10.6%) underwent re-resections, and 10 patients (6.3%) underwent re-RTx (median dose, 36.0 Gy; range, 24.0–50.0 Gy). Until the end of follow-up, 10 patients additionally received adjuvant bevacizumab in combination with TMZ after completion of the initial concomitant RTx/CTx (Table 2).[3,4] Considering all recorded complications, including oncologic, over each patient's course of treatment, a treatment-associated morbidity rate of 30.6%, affecting 49 of 160 patients, was observed.

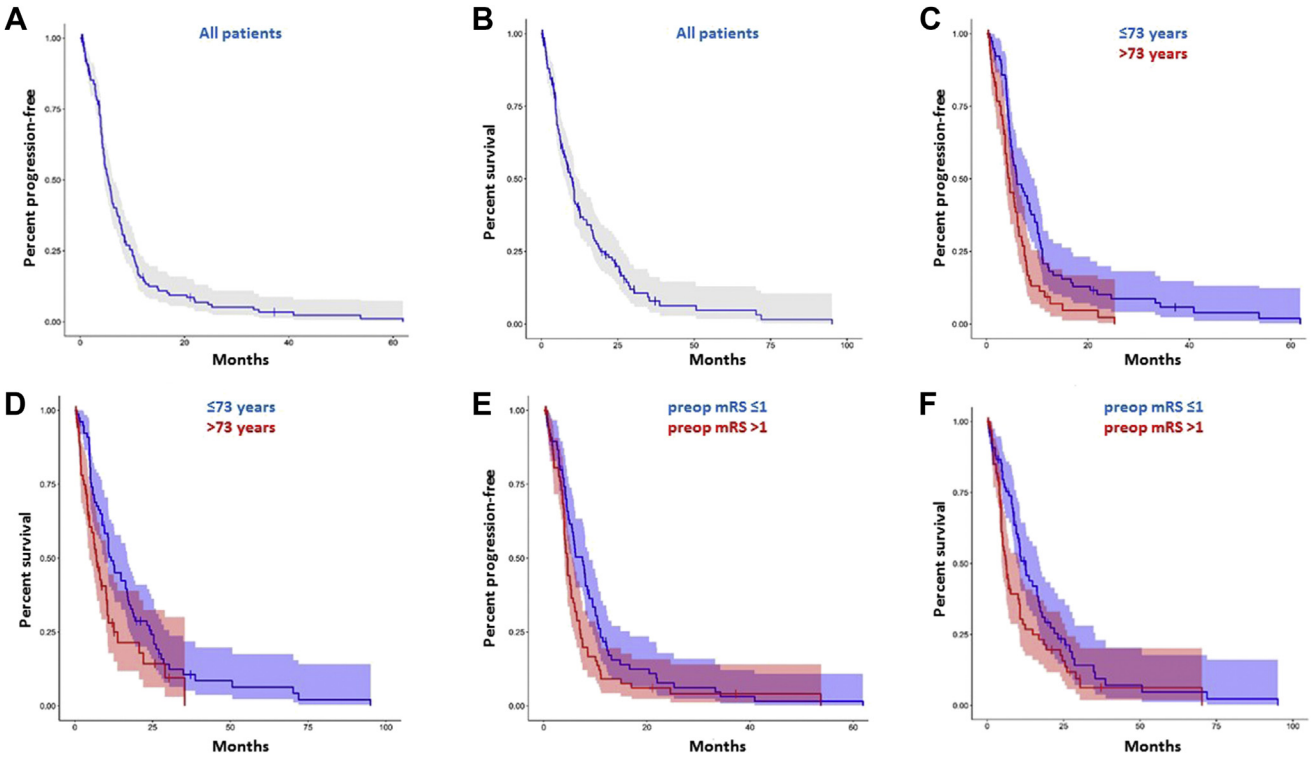

Figure 1. Survival stratified by patient age and performance status: (**A**) progression-free survival of all patients, (**B**) overall survival of all patients, (**C**) progression-free survival stratified by patient age, (**D**) overall survival stratified by patient age, (**E**) progression-free survival stratified by patient preoperative mRS score, and (**F**) overall survival stratified by patient preoperative mRS score. mRS, modified Rankin Scale.

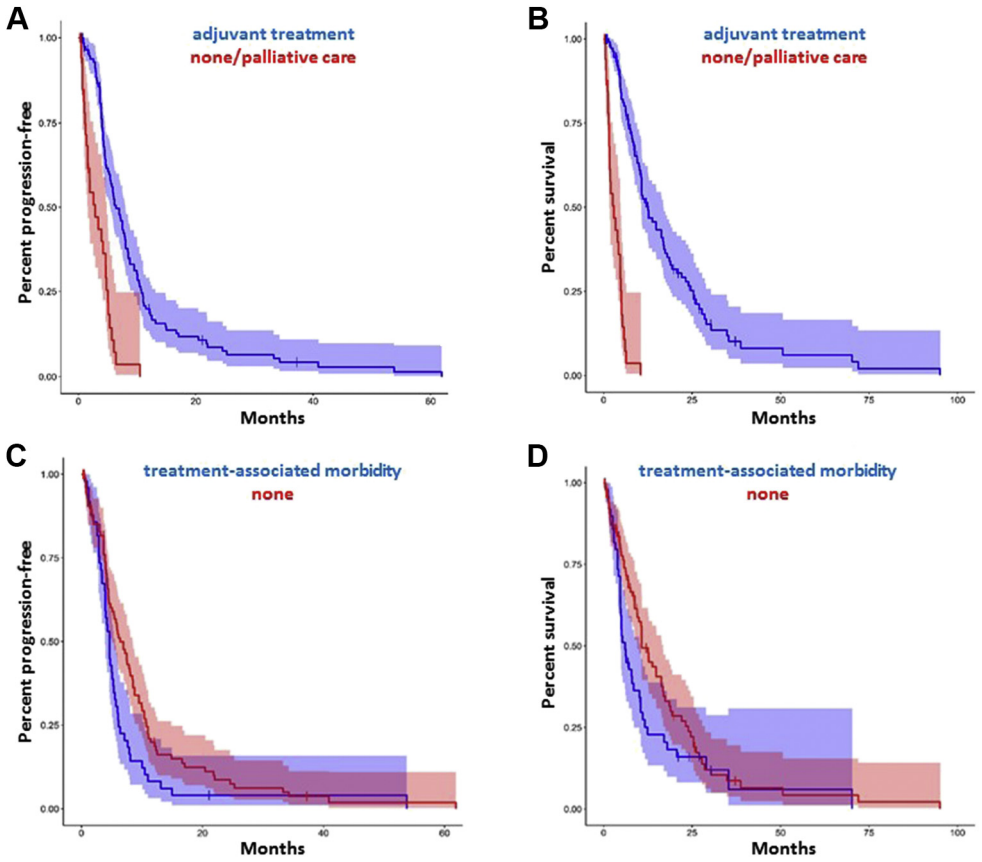

Figure 2. Survival stratified by adjuvant treatment and treatment-associated morbidity: (**A**) progression-free survival stratified by adjuvant treatment, (**B**) overall survival stratified by adjuvant treatment, (**C**) progression-free survival stratified by treatment-associated morbidity, and (**D**) overall survival stratified by treatment-associated morbidity.

Survival and Prognostic Factors

All but 4 patients (97.5%) died within the follow-up period. Median PFS and OS were 5.4 months (95% CI, 4.6–6.4 months) and 10.0 months (95% CI, 7.9–11.7 months). Favorable OS was univariately associated with patient age ≤73.0 years (11.7 months; 95% CI, 9.5–16.9 vs. 7.0 months; 95% CI, 4.6–10.5; P = 0.0083), preoperative KPS score >80% (12.8 months; 95% CI, 9.5–20.7 vs. 7.0 months; 95% CI, 5.1–10.8 months; P = 0.0179), pre- and postoperative mRS score ≤1 (12.5 months; 95% CI, 9.5–17.1 vs. 6.2 months; 95% CI, 4.9–10.7 months; P = 0.0277; and 16.3 months; 95% CI, 12.6–23.2 vs. 5.3 months; 95% CI, 4.6–7.6 months; P < 0.0001, respectively), no treatment-associated morbidity (10.8 months; 95% CI, 9.5–16.8 vs. 6.0 months; 95% CI, 4.8–10.5 months; P = 0.0478), and performance of adjuvant treatment after tumor resection (12.5 months; 95% CI, 10.6–16.9 vs. 2.9 months; 95% CI, 1.6–4.8 months; P < 0.0001) (Figures 1 and 2). The 8 patients who underwent revision surgery for postoperative hemorrhage showed shorter OS (2.3 vs. 10.5 months), and the subgroup of patients additionally receiving adjuvant bevacizumab had a longer OS of 13.0 months (95% CI, 9.8–28.0 months).

In multivariate testing, patient age ≤73.0 years (HR, 1.50; P = 0.1021), postoperative mRS score ≤1 (HR, 1.75; P = 0.0647), and adjuvant treatment (HR, 7.68; P < 0.0001) remained the strongest prognostic factors for more favorable OS (Table 2, and Figures 1 and 2). The patients' comorbidities (P = 0.3355), EOR (P = 0.5046)/postoperative tumor volume (P = 0.1272), and MGMT-promoter methylation status (P = 0.9131) were not found to impact survival (Table 3).

DISCUSSION

Older age is one of the factors for worst prognosis in patients with GBM.[4-8] Older age affects the patient's individual prognosis at multiple levels. Older adults seem to suffer from more aggressive tumor phenotypes (i.e., unfavorable biomarkers), exhibit reduced resilience (because of a comorbidity), and frequently undergo less invasive treatment (to avoid further damage). Hence, the management of elderly patients with GBM poses a true therapeutic challenge to the neuro-oncologic community.

Many neurosurgeons are hesitant to perform resections on older patients with GBM; therefore, this subgroup remains prone to

Table 3. Survival and Prognostic Factors

Survival	
Median PFS (95% CI) (months)	5.4 (4.6–6.4)
Median OS (95% CI) (months)	10.0 (7.9–11.7)

Univariate Analyses: PFS

Variable	Median (95% CI) (months)	*P* Value
Male versus female	5.1 (4.3–6.4) versus 6.0 (4.6–8.0)	0.1918
Preoperative KPS score ≤80% versus >80%	5.0 (4.3–6.4) versus 5.9 (4.5–8.8)	0.1618
Preoperative mRS score ≤1 versus >1	7.5 (5.4–8.8) versus 4.6 (4.0–5.7)	0.0259
Postoperative mRS score ≤1 versus >1	8.0 (6.0–10.4) versus 4.5 (3.8–5.2)	<0.0001
Patient age at diagnosis ≤73 versus >73 years	6.0 (5.0–9.5) versus 4.5 (3.7–6.1)	0.0017
Tumor volume ≤31.0 versus >31.0 cm^3	6.1 (4.4–7.9) versus 5.1 (4.5–6.4)	0.1801
EOR cohort (≥95% vs. 70%–94% vs. <70%)	5.3 (4.6–8.0) versus 5.9 (4.1–7.9) versus 5.0 (4.2–11.0)	0.8520
Tumor volume ≤2.4 versus >2.4 cm^3	7.5 (5.0–8.8) versus 5.5 (4.2–7.2)	0.1061
Treatment-associated morbidity versus none	4.6 (3.9–5.5) versus 6.4 (5.0–8.5)	0.0112
Adjuvant treatment versus none/palliative care	6.4 (5.4–8.0) versus 2.9 (1.6–4.8)	<0.0001
Relevant comorbidities versus none	5.1 (4.4–7.0) versus 5.7 (4.5–8.5)	0.4128
MGMT-promoter methylated versus unmethylated	5.1 (4.5–6.1) versus 4.5 (3.9–7.5)	0.6513
TERT mutated versus wild-type	5.5 (4.2–7.7) versus 5.1 (4.1–7.1)	0.6123

Univariate Analyses: OS

Variable	Median (95% CI) (months)	*P* Value
Male versus female	9.5 (6.8–16.3) versus 10.5 (7.6–14.8)	0.5375
Preoperative KPS score ≤80% versus >80%	7.0 (5.1–10.8) versus 12.8 (9.5–20.7)	0.0179
Preoperative mRS score ≤1 versus >1	12.5 (9.5–17.1) versus 6.2 (4.9–10.7)	0.0277
Postoperative mRS score ≤1 versus >1	16.3 (12.6–23.2) versus 5.3 (4.6–7.6)	<0.0001
Patient age at diagnosis ≤73 versus >73 years	11.7 (9.5–16.9) versus 7.0 (4.6–10.5)	0.0083
Tumor volume ≤31.0 versus >31.0	10.8 (8.0–17.9) versus 9.5 (5.7–12.4)	0.1184
EOR cohort (≥95% vs. 70%–94% vs. <70%)	8.8 (5.4–14.9) versus 10.7 (8.8–16.9) versus 11.7 (7.0–NA)	0.5046
Postoperative tumor volume ≤2.4 versus >2.4	13.7 (10.0–20.7) versus 10.7 (7.6–16.3)	0.1272
Treatment-associated morbidity versus none	6.0 (4.8–10.5) versus 10.8 (9.5–16.8)	0.0478
Adjuvant treatment versus none/palliative care	12.5 (10.6–16.9) versus 2.9 (1.6–4.8)	<0.0001
Relevant comorbidities versus none	8.5 (6.8–10.8) versus 10.8 (7.6–16.9)	0.3355
MGMT-promoter methylated versus unmethylated	9.5 (6.3–12.8) versus 8.8 (5.7–16.3)	0.9131
TERT mutated versus wild-type	9.5 (7.0–18.6) versus 8.8 (6.3–11.7)	0.4067

Multivariate Analysis: PFS

Variable	Hazard Ratio (95% CI)	*P* Value
Preoperative mRS score >1 versus ≤1	1.13 (0.72–1.78)	0.5882
Postoperative mRS score >1 versus ≤1	1.57 (0.97–2.54)	0.0691
No treatment/palliative care versus adjuvant treatment	2.64 (1.55–4.51)	0.0004

Continues

Table 3. Continued

Multivariate Analysis: PFS		
Variable	**Hazard Ratio (95% CI)**	***P* Value**
Treatment-associated morbidity (yes vs. no)	1.06 (0.68–1.65)	0.7857
Patient age at diagnosis >73 versus >73 years	1.53 (1.04–2.24)	0.0291
Multivariate Analysis: OS		
Variable	**Hazard Ratio (95% CI)**	***P* Value**
Preoperative KPS score >80% versus ≤80%	0.79 (0.39–1.62)	0.5233
Preoperative mRS score >1 versus ≤1	0.90 (0.40–2.04)	0.8023
Postoperative mRS score >1 versus ≤1	1.75 (0.97–3.16)	0.0647
No treatment/palliative care versus adjuvant treatment	7.68 (4.06–14.56)	<0.0001
Treatment-associated morbidity versus none	1.52 (0.92–2.49)	0.0993
Patient age at diagnosis >73 versus ≤73 years	1.50 (0.92–2.45)	0.1021

PFS, progression-free survival, CI, confidence interval; OS, overall survival, KPS, Karnofsky Performance Status Scale; mRS, modified Rankin Scale; EOR, extent of resection; MGMT, O(6)-methylguanine-DNA methyltransferase; NA, limit not available.

undertreatment. Identifying the subgroup of elderly patients, which might tolerate a more aggressive treatment with favorable influence on prognosis, is of paramount importance. Data on this topic are still scarce. This particularly concerns the impact of microsurgical resections in the light of modern biomarker profiling.

This study adds to the existing level of knowledge regarding these important aspects of neuro-oncologic treatment. In summary, our data point to the following clinical implications for the therapeutic management of elderly patients with GBM. In selected patients, 1) tumor resections can be conducted with a tolerable risk for surgery-related morbidity; 2) a timely start of adjuvant treatment after initial surgery seems to be feasible; 3) adjuvant treatment may even include RTx/CTx according to the Stupp protocol; 4) clinical outcome, however, remains limited with survival of approximately 10 months; and 5) age at diagnosis, performance status, adjuvant treatment, and treatment-associated morbidity still remain the strongest predictors for OS.

The EORTC/NCIC protocol is the standard pattern of care for patients newly diagnosed with GBM who are <65 years of age.[1] Improved understanding of the tumor's biomarker profile has led to more stratified and nuanced treatments. Especially, MGMT-methylation status has gained significant relevance when deciding on the chemosensitivity and presumed benefit from additional TMZ administration.[1] The Nordic trial reported only little benefit from adjuvant TMZ treatment in older adults with unmethylated GBM, and the authors recommended treatment stratification between TMZ and percutaneous radiotherapy based on MGMT status.[11]

In our population, we recorded median PFS and OS of 5.4 and 10.0 months, respectively. Even though these survival rates may seem discouraging at first sight, they are in accordance with reported outcomes. For reference, the aforementioned Nordic trial resulted in a median OS of 9.6 months in case of radiotherapy and 8.6 months for TMZ.[11] Other groups recorded a median OS ranging from only 3.8 to 5.6 months[7,19,24]; more recently, Heiland et al.[20] reported a median survival of 7.5 months for 342 elderly patients with GBM who were ≥65 years of age. A Finnish nationwide study including patients >70 years of age reported a survival of 4.5 months for individuals diagnosed between 2007 and 2013.[4] Furthermore, one has to keep in mind that for unselected cohorts, regarding patient age, the survival still lies in the range of merely approximately 12–15 months.[1] Moreover, almost all of the patients in this study suffered from wild-type *IDH* 1/2 GBM, which is notably associated with poor prognosis and typical for elderly patient populations.[2,9] The presented cohort consisted, however, of selected cases with good preoperative performance status, which were deemed suitable for resection regarding the patients' condition and tumor location; patients who underwent stereotactic biopsy were not evaluated. Therefore, our dataset does not allow for conclusions regarding this subgroup and/or patients with poor clinical status. Additionally, adjuvant treatment was not stratified by MGMT-promoter methylation.

Then again, this provides for interesting additional aspects. Notably, most patients (60.0%) underwent concomitant and adjuvant RTx/CTx, which is considered the most aggressive treatment for patients with GBM, especially for those of higher age. Nonetheless, chemotherapy-associated morbidity was within a tolerable range (19.4%). Adjuvant treatment could be started within a prompt time frame (median, 24 days), and patients did not require prolonged recovery after neurosurgery. No prospective study has yet evaluated the effects of the EORTC/NCIC protocol in elderly patients. Despite generally good postoperative status, and an EOR and surgery-related morbidity within the usual range for patients with GBM, our outcome was worse than in younger

cohorts.[1,35-37] Therefore, it has to be assumed that the benefit of aggressive adjuvant treatment appears to decrease with patient age. Furthermore, it has to be acknowledged that a considerable proportion of the patients (23.8%) only received BSC after resections and treatment-associated morbidity led to a significantly worse survival. This underscores the difficulty to predict which patients are suitable candidates for aggressive treatment.

Another aspect of our study was to identify prognostic factors to optimize this patient selection. Our analyses showed that younger patient age, better performance status, and adjuvant treatment were found to be the strongest predictors of prolonged survival, which is in line with the existing literature.[5,7,20,24,28] Interestingly, neither the MGMT-promoter methylation status nor the EOR were found to be of significance. These findings were unexpected because they appear to contradict existing data.[1,5-7,10,11,17,18,20,28,38] Although the issue of MGMT-promoter methylation is not, or insufficiently, addressed by many studies, the MGMT-promoter methylation status has been shown to remain a prognostic factor also for elderly patients.[4,7,11,14,20] In addition, older adults have usually been found to benefit from an increased EOR (e.g., Heiland et al.[20] reported an increased median OS of 10.8 months for their subgroup of cases with GTR, Babu et al.[5] recorded an OS of 14.1 months for GTR compared with only 9.1 months for subtotal resection, Zhang et al.[18] recently also found GTR to be significantly associated with longer OS compared with subtotal resection [15 vs. 10.5 months, respectively] in a cohort of 70 elderly patients with GBM).[10,18,28] Additional correlation analyses revealed that MGMT-promoter methylation was coincidentally associated with higher treatment-associated morbidity over the course of treatment ($P = 0.0031$). An important limitation of our data hereby is that the MGMT-promoter methylation status was not available for all patients (118 of 160) and the proportion of MGMT-methylated tumors (62.7%) was higher than usually reported.[20] As previously stated, adjuvant treatment was not influenced by the MGMT status, which might also contribute as a confounder. Moreover, increased EOR was found to correlate with increased treatment-associated morbidity ($P = 0.0025$). Patients with methylated MGMT-status and/or patients with increased EOR were not of older age, had worse preoperative performance status, or underwent less adjuvant treatment. These 2 important aspects implicate that treatment-associated complications significantly determine the outcome, and may thereby even outweigh any potential benefits of increased EOR and favorable biomarkers. The fact that treatment-associated morbidity only achieved significance in univariate ($P = 0.0478$) but not in multivariate testing (HR, 1.52; $P = 0.0993$) can best be explained by the relatively low number of events, which did not allow to integrate interaction terms in the Cox model. Especially, the aspect of the correlation between EOR and treatment-associated morbidity is of importance because in contrast with MGMT status, it is a direct consequence of the surgical intervention and can thereby be seen as a modifiable factor. Patients with postoperative hemorrhage were neither found to be of older age (median age, 74.5 vs. 73.2 years) nor suffered from substantially larger tumors (median tumor volume, 33.4 vs. 30.5 cm^3), respectively.

To objectively assess the treatment burden, we analyzed the treatment-associated morbidity rate and postoperative hospitalization. Surgery-associated morbidity was seen in approximately 10% and the overall treatment-associated morbidity reached approximately 30%. This appears to be similar to those of younger patients with GBM.[36] Only a few studies on older adults provide precise numbers regarding complications. D'Amico et al.[22] reported a surgery-related overall complication rate of 21.9% after craniotomy of elderly patients with GBM, and Karsy et al.[39] recorded 34 complications in 23 patients, stating that increased EOR was only significantly associated with improved survival in patients without complications. The median required postoperative hospital stay was 8 days, not substantially longer than for unselected patients with glioma. Flanigan et al.[23] also reported a mean in-hospital stay of 6.3 days for elderly patients. However, any treatment-associated morbidity will undeniably prolong hospitalization.

We found that survival of elderly patients with GBM is still <1 year. The patients, nonetheless, generally tolerated adjuvant aggressive treatment; treatment-associated morbidity and the surgical treatment burden were moderate. The benefit of resection within the framework of multimodal treatment and biomarker stratification, however, still has to be clarified in future prospective studies.

CONCLUSIONS

Clinical outcome for elderly patients with GBM remains limited. Nonetheless, the observed treatment-associated morbidity and treatment burden were moderate in the patients. Patient age, performance status, adjuvant treatment, and treatment-associated morbidity remain the strongest predictors for survival. If treatment-associated morbidity occurred, however, it led to significant shorter survival. Based on our findings, we think there should not be therapeutic nihilism even in patients of older age. The risks and benefits of resections within the framework of modern biomarker-stratified treatment concepts require further evaluation in future prospective data.

REFERENCES

1. Louis DN, Ohgaki H, Wiestier OD, et al., eds. *WHO Classification of Tumours of the Central Nervous System*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2016.

2. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997-1003.

3. Arvold ND, Reardon DA. Treatment options and outcomes for glioblastoma in the elderly patient. *Clin Interv Aging*. 2014;9:357-367.

4. Korja M, Raj R, Seppä K, et al. Glioblastoma survival is improving despite increasing incidence rates: a nationwide study between 2000 and 2013 in Finland. *Neuro Oncol*. 2018;21:370-391.

5. Babu R, Komisarow JM, Agarwal VJ, et al. Glioblastoma in the elderly: the effect of aggressive and modern therapies on survival. *J Neurosurg*. 2016;124:998-1007.

6. Ewelt C, Goeppert M, Rapp M, et al. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. *J Neurooncol*. 2011;103:611-618.

7. Tanaka S, Meyer FB, Buckner JC, et al. Presentation, management, and outcome of newly diagnosed glioblastoma in elderly patients. *J Neurosurg*. 2013;118:786-798.

8. Harris G, Jayamanne D, Wheeler H, et al. Survival outcomes of elderly patients with glioblastoma multiforme in their 75th year or older treated with adjuvant therapy. *Int J Radiat Oncol Biol Phys*. 2017; 98:802-810.

9. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360: 765-773.

10. Lombardi G, Pace A, Pasqualetti F, et al. Predictors of survival and effect of short (40 Gy) or standard-course (60 Gy) irradiation plus concomitant temozolomide in elderly patients with glioblastoma: a multicenter retrospective study of AINO (Italian Association of Neuro-Oncology). *J Neurooncol*. 2015;125:359-367.

11. Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol*. 2012;13:916-926.

12. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol*. 2004;22:1583-1588.

13. Guedes de Castro D, Matiello J, Roa W, et al. Survival outcomes with short-course radiation therapy in elderly patients with glioblastoma: data from a randomized phase 3 trial. *Int J Radiat Oncol Biol Phys*. 2017;98:931-938.

14. Glaser SM, Dohopolski MJ, Balasubramani GK, et al. Glioblastoma multiforme (GBM) in the elderly: initial treatment strategy and overall survival. *J Neurooncol*. 2017;134:107-118.

15. Morgan ER, Norman A, Laing K, et al. Treatment and outcomes for glioblastoma in elderly compared with non-elderly patients: a population-based study. *Curr Oncol*. 2017;24:e92-e98.

16. Straube C, Scherb H, Gempt J, et al. Does age really matter? Radiotherapy in elderly patients with glioblastoma, the Munich experience. *Radiat Oncol*. 2017;12:77.

17. Liu YL, Liu PF, Shao W, et al. Effect of temozolomide on survival in elderly patients with glioblastoma and impaired performance status: a propensity score-matching analysis. *Onco Targets Ther*. 2017;10:4029-4035.

18. Zhang C, Wang X, Hao S, et al. Analysis of treatment tolerance and factors associated with overall survival in elderly patients with glioblastoma. *World Neurosurg*. 2016;95:77-84.

19. Vuorinen V, Hinkka S, Färkkilä M, et al. Debulking or biopsy of malignant glioma in elderly people - a randomised study. *Acta Neurochir (Wien)*. 2003;145:5-10.

20. Heiland DH, Haaker G, Watzlawick R, et al. One decade of glioblastoma multiforme surgery in 342 elderly patients: what have we learned? *J Neurooncol*. 2018;140:385-391.

21. Cunha MLVD, Esmeraldo ACS, Henriques LAW, et al. Elderly patients with glioblastoma: the impact of surgical resection extent on survival. *Rev Assoc Med Bras (1992)*. 2019;65:937-945.

22. D'Amico RS, Cloney MB, Sonabend AM, et al. The safety of surgery in elderly patients with primary and recurrent glioblastoma. *World Neurosurg*. 2015; 84:913-919.

23. Flanigan PM, Jahangiri A, Kuang R, et al. Developing an algorithm for optimizing care of elderly patients with glioblastoma. *Neurosurgery*. 2018;82: 64-75.

24. Lorimer CF, Hanna C, Saran F, et al. Challenges to treating older glioblastoma patients: the influence of clinical and tumour characteristics on survival outcomes. *Clin Oncol (R Coll Radiol)*. 2017; 29:739-747.

25. Lorimer CF, Saran F, Chalmers AJ, et al. Glioblastoma in the elderly - how do we choose who to treat? *J Geriatr Oncol*. 2016;7:453-456.

26. Zanello M, Roux A, Ursu R, et al. Recurrent glioblastomas in the elderly after maximal first-line treatment: does preserved overall condition warrant a maximal second-line treatment? *J Neurooncol*. 2017;135:285-297.

27. Tsang DS, Khan L, Perry JR, et al. Survival outcomes in elderly patients with glioblastoma. *Clin Oncol (R Coll Radiol)*. 2015;27:176-183.

28. Hoffermann M, Bruckmann L, Kariem Mahdy A, et al. Treatment results and outcome in elderly patients with glioblastoma multiforme–a retrospective single institution analysis. *Clin Neurol Neurosurg*. 2015;128:60-69.

29. Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol*. 2017;18:e315-e329.

30. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28: 1963-1972.

31. Albert NL, Weller M, Suchorska B, et al. Response assessment in neuro-oncology working group and European Association for neuro-oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro Oncol*. 2016;18:1199-1208.

32. The R Project for statistical Computing. Available at: https://www.R-project.org/. Accessed July 3, 2019.

33. The R Project for statistical Computing. Available at: https://cran.r-project.org/web/packages/survival/index.html. Accessed July 3, 2019.

34. Chinot OL, de La Motte Rouge T, Moore N, et al. AVAglio: phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. *Adv Ther*. 2011;28: 334-340.

35. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol*. 2006;7:392-401.

36. Stummer W, Tonn JC, Mehdorn HM, et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. Clinical article. *J Neurosurg*. 2011;114:613-623.

37. Sanai N, Polley MY, McDermott MW, et al. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg*. 2011;115:3-8.

38. Park M, Lee SK, Chang JH, et al. Elderly patients with newly diagnosed glioblastoma: can preoperative imaging descriptors improve the predictive power of a survival model? *J Neurooncol*. 2017;134: 423-431.

39. Karsy M, Yoon N, Boettcher L, et al. Surgical treatment of glioblastoma in the elderly: the impact of complications. *J Neurooncol*. 2018;138: 123-132.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 23 July 2019; accepted 18 September 2019

Citation: World Neurosurg. (2020) 133:e583-e591. https://doi.org/10.1016/j.wneu.2019.09.097

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

1878-8750/$ - see front matter